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Percutaneous tibial nerve stimulation versus tolterodine for overactive bladder in women: a randomised controlled trial

Oliver Preyer [a,*], Wolfgang Umek [b], Thomas Laml [b], Vesna Bjelic-Radisic [c], Boris Gabriel [d], Martina Mittlboeck [e], Engelbert Hanzal [b]

[a] Zell am See Hospital, Department of Obstetrics & Gynaecology, Paracelsusstrasse 8, A-5700 Zell am See, Austria
[b] Medical University of Vienna, Department of Obstetrics & Gynaecology, Division of General Gynaecology and Gynaecologic Oncology, Waehringer Guertel 18-20, A-1090 Vienna, Austria
[c] Medical University of Graz, Department of Obstetrics & Gynaecology, Division of Gynaecology, Auenbrugger Platz 14, A-8036 Graz, Austria
[d] University Hospital Freiburg, Department of Obstetrics & Gynaecology, Division of Gynaecology, Hugstetter Strasse 44, D-79106 Freiburg, Germany
[e] Medical University of Vienna, Centre for Medical Statistics, Informatics, and Intelligent Systems, Section for Clinical Biometrics, Spitalgasse 23, A-1090 Vienna, Austria

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ABSTRACT

Objective: We performed a randomised controlled trial of percutaneous tibial nerve stimulation (PTNS) versus tolterodine for treating treatment naïve women with overactive bladder (OAB).
Study design: 36 patients with symptoms of OAB were randomised to 3 months of treatment with weekly PTNS or tolterodine (2 mg bid p.o.). The primary outcome measure was the difference of micturitions per 24 h. The secondary outcome measure was the impact on quality of life (QoL) measured with a visual analogue scale (VAS) between baseline and after 3 months of therapy.
Results: Micturition frequencies did not decline significantly ($p = 0.13$) over time and there were no significant treatment differences ($p = 0.96$). QoL was significantly dependent from its level at baseline ($p = 0.002$) and showed improvement over time compared to baseline measurements but no significant differences between both treatment groups ($p = 0.07$). Incontinence episodes per 24 h depended significantly on the level at baseline ($p = 0.0001$) and declined significantly ($p = 0.03$) during 3 months of therapy in both therapy groups. However no significant treatment differences on the reduction of incontinence episodes in 24 h could be shown between both therapy groups ($p = 0.89$). PTNS had fewer side effects than tolterodine ($p = 0.04$).
Conclusion: PTNS and tolterodine were both effective in reducing incontinence episodes and improving QoL in patients with OAB but not micturition frequencies. PTNS had fewer side effects.

Introduction

Overactive bladder syndrome (OAB) is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence [1,2] affecting about 16–45% of adult women, with an age-related increase of prevalence [3–5]. OAB significantly impacts quality of life (QoL) and can cause social isolation and morbidity due to falls and fractures [6]. First-line therapy is conservative and includes behavioural therapy, pelvic floor muscle training (PFMT), and anticholinergics [7]. However, limited efficacy and side effects are an impetus for the development of alternative treatments.

Percutaneous tibial nerve stimulation (PTNS), first described by Stoller et al. [8] in 1999, is a minimally invasive and comparatively inexpensive option for the treatment of OAB [9]. Electrical stimulation of the tibial nerve at the medial malleolus leads to stimulation of the sacral segments S2 and S3, where the spinal centre for bladder control is located.

Previous studies, some of them placebo controlled, have shown positive effects of PTNS on OAB symptoms, urodynamic findings and QoL without serious adverse events [10]. In a recent Cochrane review of anticholinergics versus non-drug active therapies for

Abbreviations: OAB, overactive bladder syndrome; PTNS, percutaneous tibial nerve stimulation; RCT, randomised controlled trial; QoL, quality of life; VAS, visual analogue scale; p.o., per os; SAE, serious adverse event; EC, ethics committee; ICS, International Continence Society; SD, standard deviation; SNS, sacral neurostimulation.

* Corresponding author. Tel.: +43 6542 777 2510; fax: +43 6542 777 2515.
E-mail address: oliver.preyer@kh-zellamsee.at (O. Preyer).

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non-neurogenic overactive bladder syndrome by Rai et al., subjective improvement rates tended to favour the electrical stimulation group. Statistical significance was shown only for PTNS [11].

Side effects of PTNS include slight bleeding, haematoma and pain at the site of needle insertion. The present multicentre prospective randomised controlled trial (RCT) was designed as pilot study to show a difference in the efficacy and side effects of PTNS versus an oral anticholinergic agent for treating OAB in women over a 3 months period.

Materials and methods

We followed the CONSORT guidelines in planning and conducting this RCT [12]. A provisional power calculation based on an exaggerated difference of 20% was performed for this pilot study. A reduction from a mean micturition per 24 h after a 3 months treatment with tolterodine of 13–10.4 under PTNS (assuming a common standard deviation of 2.7) could have been detected with 80% power and a two-sided significance level of 5% with 18 patients per group.

Inclusion criteria of the study were: female; minimum age of 18 years; complaints of OAB dry or wet consistent with the IUGA/ICS criteria; no prior treatment with PTNS or anticholinergics; Data were collected at the urogynaecologic consultation hours of the participating gynaecologic departments.

Exclusion criteria were: pregnancy or intention to become pregnant during the study period; active or recurrent urinary tract infections (more than 4 per year); residual urine of more than 100 ml; history of urinary fistula, bladder or kidney stones, interstitial cystitis; history of cystoscopic abnormalities or possible malignancy, diabetes mellitus, cardiac pacemaker or implanted defibrillator; history of anatomic or posttraumatic malformations of the lower limbs; immobility; contraindications for anticholinergics or PTNS; disability to understand the study requirements and procedures, advantages and possible side effects.

Patients were screened for the ability to participate in our trial and randomised into two parallel treatment arms (PTNS vs. tolterodine) at three centres in Austria and Germany. The ethics committees of the participating institutions approved the study protocol.

A pertinent history was obtained by the urogynecologist and an urogynaecologic examination was performed consisting of urine check, residual volume check, vaginal examination and inspection, and full urodynamic work up.

Allocation concealment. The patients and assessors were not blinded.

Randomisation was centralised by telephone and the random allocation sequence was generated by computer assistance using a method of adaptive randomisation. This method guarantees a balance of stratification criteria to the treatment group and the sample sizes of the treatment groups (1:1) [13] to receive PTNS or tolterodine (2 mg bid p.o.) through 3 months.

Stratification for randomisation was done for micturitions per 24 h (0–8, 9–12, 13–24, ≥25), incontinence episodes in 24 h (0–2, 3–10, 11–18, 19–24, ≥25), age (18–44, 45–55, 56–65, ≥66 years), and smoking.

The assessment of patients and interventions are shown in Fig. 1. The primary outcome criteria were the difference of micturitions per 24 h (voiding diaries) in between the two groups. Secondary outcome criteria were the symptom impact on QoL. All patients provided signed informed consent before being included into the study. The reporting time between randomisation and start of treatment was 0–14 days.

Intervention, Symptom impact on QoL assessment and final evaluation were structured as follows.

(1) Intervention

Patients randomised to PTNS were seen once weekly for a 30-min session. PTNS was performed as described by Stoller et al. [5] and Vandoninck et al. (Urgent PC® device by Uroplasty™) [14] (Fig. 2). All PTNS-treatments were administered by equally trained urogynecologists. Women randomised to tolterodine were prescribed 2 mg twice-daily p.o. All patients received information on timed voiding.

(2) Symptom impact on QoL assessment

At an interim evaluation at one month all patients completed symptom-based QoL-VAS (assessing criteria for OAB as defined by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) [1]), were asked for side effects and underwent an examination including urodynamics and evaluation of their 3-day voiding diaries at baseline and at 1 and 3 months (Fig. 1).

A global response assessment (GRS) was performed with visual analogue scale measuring the symptom impact on QoL and patients were asked to which extent the defined symptom showed an impact on their QoL (VAS 0 = no negative impact on QoL, 10 = most negative impact on QoL). A change of 2 points was considered as minimal clinically important difference for the VAS [15].

(3) Final evaluation

Patients were followed for 3 months. The study was stopped when 18 patients in each treatment arm were included. Non-responders had the option to switch treatments. At 3 months all remaining patients were fully re-evaluated to the extent of examination at baseline regarding the primary endpoint of the study and were asked for side effects.

Data analyses

VAS and voiding diary results were analysed by an urogynecologist not involved in recruitment or treatment of patients.

Statistical analyses

Categorical data are described with absolute frequencies and percentages and group differences were tested with a chi-square test. Continuous data are described with mean and standard deviation (±SD) in case of normally distributed data (graphical inspection) and with median (minimum, maximum) otherwise. Micturitions and incontinence episodes in 24 h and QoL are modelled with a linear mixed model with repeated measurements, assuming a first order autoregressive variance–covariance matrix. Explanatory variables in the model were: baseline value (before treatment), point in time of measurements (1 and 3 months) and treatment group. Interactions between time and treatment groups were also tested. Modelling assumptions (normal distribution and homoskedasticity) are investigated by residual plots. In case of a right skew distribution of incontinence episodes in 24 h, a logarithmic transformation is applied to the number of incontinence episodes plus 1, in order to achieve a normally distributed and homoscedastic residual pattern. Comparisons of baseline values and values under treatment were performed either by paired *t*-tests in case of normally distributed differences or by Wilcoxon's signed rank test otherwise. All results are two-sided and $p \leq 0.05$ was considered statistical significant. All calculations were performed using SAS software version 9.3.

Results

126 patients were screened for the ability to participate in our trial. 36 Patients were randomised into two parallel treatment arms (PTNS vs. tolterodine). 18 patients received PTNS and 18